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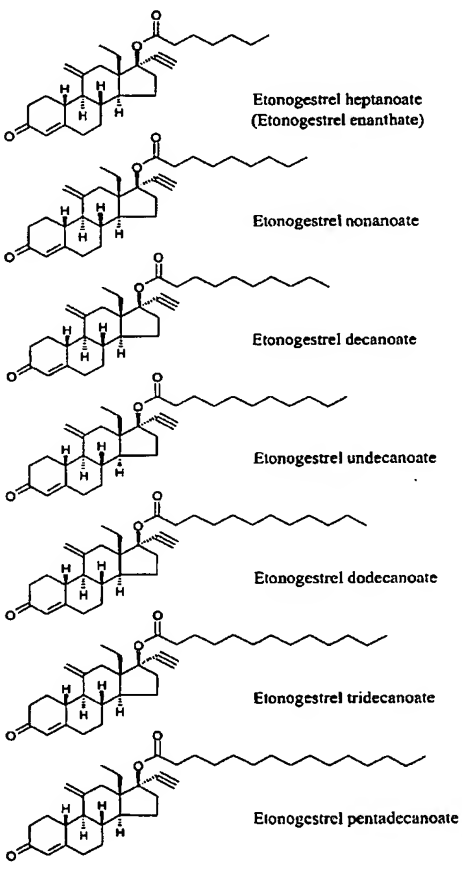
(54) Title: NEW ETONOGESTREL ESTERS



(57) Abstract: The subject invention provides new progestogen esters and uses thereof.

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 737 477 A (AKZO NOBEL NV) 16 October 1996 (1996-10-16) the whole document ---	1-10,16
Y	DE 196 13 698 A (SCHERING AG) 23 January 1997 (1997-01-23) the whole document ---	1-10,16
A	EP 0 129 947 A (WORLD HEALTH ORG) 2 January 1985 (1985-01-02) the whole document --- -/--	1,3

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GUERIN J F ET AL: "INHIBITION OF SPERMATOGENESIS IN MEN USING VARIOUS COMBINATIONS OF ORAL PROGESTAGENS AND PERCUTANEOUS OR ORAL ANDROGENS" INTERNATIONAL JOURNAL OF ANDROLOGY, BLACKWELL SCIENTIFIC PUBLICATIONS, OXFORD, GB, vol. 11, no. 3, 1988, pages 187-199, XP000917371 ISSN: 0105-6263 cited in the application the whole document	3

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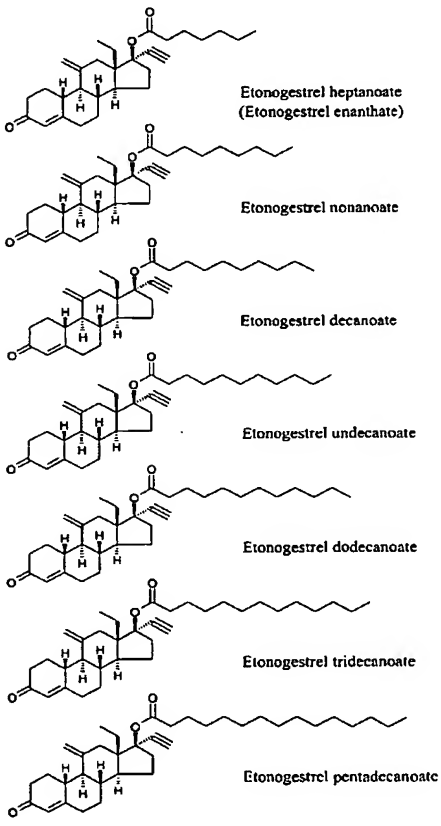
(54) Title: NEW ETONOGESTREL ESTERS

(57) Abstract: The subject invention provides new progestogen esters and uses thereof.



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NEW ETONOGESTREL ESTERS

FIELD OF THE INVENTION

The subject invention concerns the field of (female and male) contraception, (female and male) hormone replacement therapy (HRT) and treatment/prevention of gynaecological disorders.

BACKGROUND

Contraceptive methods for men and women are important for worldwide reproductive health.

However, no effective and efficient methods of male contraception are as of yet available.

Male contraception seeks to suppress spermatogenesis through the suppression of the gonadotropins lutcinizing hormone (LH) and follicle-stimulating hormone (FSH). This results in a depletion of intratesticular testosterone and cessation of spermatogenesis.

Administration of progestagen results in a dose dependent suppression of pituitary gonadotrophins and consequently, a decrease in testosterone levels and a reversible inhibition of spermatogenesis. An exogenous androgen is required to compensate for the reduced testosterone levels. In the same way, male HRT can be accomplished, resulting in replacement of testosterone by an exogenous androgen which is safer on the prostate than endogenous testosterone.

The use of progestogens together with androgens for use as male contraceptives is known (Guerin and Rollet (1988), International Journal of Andrology 11, 187-199).

However, the use of specific esters of etonogestrel for male contraception and male HRT has not been suggested.

In addition, the use of progestogens together with estrogens for use in female contraception is known (M. Tausk, J.H.H. Thijssen, Tj.B. van Wimersma Greidanus, "Pharmakologie der Hormone", Georg Thieme Verlag, Stuttgart, 1986).

Progestagens are widely used for female contraception and in female HRT. In contraception, the combination progestagen-estrogen oral contraceptives are the most widely used. Administration of such a combination results in a number of effects: it blocks ovulation, it interferes with phasic development of the endometrium which decreases the chance for successful implantation, and it causes the cervical mucus to become so viscous that it hinders sperm penetration. Most progestagen-only-pills (POP's) aim at the last mentioned effect only.

Female HRT is aimed at suppletion of endogenous estrogen for the treatment of peri- and postmenopausal complaints (hot flushes, vaginal dryness), and for prevention of symptoms of long-term estrogen deficiency. The latter include osteoporosis, coronary artery disease, urogenital incontinence, and possibly also Alzheimer's disease and colorectal cancer. A drawback of long-term unopposed estrogen administration is the associated increase in endometrium proliferation, which in turn may increase the risk of endometrial cancer. For that reason, progestagens are co-administered in long-term regimes, because of their ability to reduce the proliferative activity of endometrial epithelium and to induce secretory conversion.

However, the use of specific esters of etonogestrel for female contraception, female HRT and treatment/prevention of gynaecological disorders has not been suggested.

The subject invention describes new esters of etonogestrel, i.e. etonogestrel decanoate, etonogestrel undecanoate, and etonogestrel dodecanoate which have surprisingly been found to have a better pharmacokinetic profile than other etonogestrel esters. These esters enable a single-dose administration of a progestogen with a long duration of action.

SUMMARY OF THE INVENTION

The subject invention provides new progestogen esters, i.e. etonogestrel decanoate, etonogestrel undecanoate, and etonogestrel dodecanoate and uses thereof for both male and female contraception and male and female HRT.

In addition, the use of these esters for treatment and prevention of female gynaecological disorders such as endometriosis, menorrhagia, meno-metrorrhagia, pre-menstrual syndrome and dysmenorrhoea are also contemplated.

FIGURES

Figure 1

Chemical structures of etonogestrel heptanoate (etonogestrel enanthate), etonogestrel nonanoate, etonogestrel decanoate, etonogestrel undecanoate, etonogestrel dodecanoate, etonogestrel tridecanoate, and etonogestrel pentadecanoate.

Figure 2a

Effect of one intramuscular (IM) injection of etonogestrel, etonogestrel heptanoate (etonogestrel enanthate), etonogestrel nonanoate and etonogestrel undecanoate on plasma levels of etonogestrel in male intact rabbits. Means and SEM of N=3.

Figure 2b

Effect of one intramuscular (IM) injection of etonogestrel heptanoate (etonogestrel enanthate), etonogestrel nonanoate, etonogestrel decanoate, etonogestrel undecanoate, etonogestrel dodecanoate, etonogestrel tridecanoate on plasma levels of etonogestrel in male intact rabbits. Means and SEM of N=3.

DETAILED DESCRIPTION OF THE INVENTION

The subject invention provides the compounds etonogestrel decanoate, etonogestrel undecanoate, and etonogestrel dodecanoate.

The subject invention contemplates a contraceptive and/or HRT kit comprising a contraceptively and/or therapeutically effective amount of etonogestrel decanoate and/or etonogestrel undecanoate and/or etonogestrel dodecanoate for both male and female contraception and HRT.

The subject invention further provides a use of a contraceptively and/or therapeutically effective amount of etonogestrel decanoate and/or etonogestrel undecanoate and/or etonogestrel dodecanoate for the preparation of a medicament for contraception and/or HRT. In a preferred embodiment, the medicament is for male contraception and/or male HRT. In another embodiment, the medicament is for female contraception and/or female HRT.

The subject invention further contemplates a method of contraception and/or HRT comprising administering to a subject a contraceptively and/or therapeutically effective amount of etonogestrel decanoate and/or etonogestrel undecanoate and/or etonogestrel dodecanoate. In a preferred embodiment, the subject is a male subject. In another embodiment, the subject is a female subject.

The subject invention additionally provides a use of a therapeutically effective amount of etonogestrel decanoate and/or etonogestrel undecanoate and/or etonogestrel dodecanoate for the preparation of a medicament for the treatment and/or prevention of female gynaecological disorders such as endometriosis, menorrhagia, meno-metrorrhagia, pre-menstrual syndrome and dysmenorrhoea.

The subject invention further contemplates a method of treatment and/or prevention of female gynaecological disorders such as endometriosis, menorrhagia, meno-metrorrhagia, pre-menstrual syndrome and dysmenorrhoea comprising administering to a female subject a therapeutically effective amount of etonogestrel decanoate and/or etonogestrel undecanoate and/or etonogestrel dodecanoate.

The compounds of the subject invention can be administered via any suitable route available to the skilled person.

In the case of oral administration, a solid dosage unit such as a tablet or a capsule is contemplated. The compounds of the invention can be formulated with a pharmaceutically acceptable carrier, such as described in the standard reference, Gennaro *et al*, *Remmington: The Science and Practice of Pharmacy*, (20th ed., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing). The compounds of the invention and the pharmaceutically acceptable carrier may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, *e.g.* nasal spray. For making dosage units, *e.g.* tablets, the use of conventional additives such as fillers, colorants, polymeric binders, lubricants, flow enhancers, glidants and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and the like.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

The dose of and regimen of administration of the compounds of the invention, or a pharmaceutical composition thereof, to be administered will depend on the therapeutic effect to be achieved and will vary with the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered, and/or the particular contraceptive or HRT regimen in which it is used. Typical dosage amounts are 0.001-5 mg per kg body weight.

The present invention is further described in the following example which is not in any way intended to limit the scope of the invention as claimed.

EXAMPLE - Kinetics of etonogestrel C7, C9, C10, C11, C12 and C13 esters in rabbits

The following etonogestrel esters were prepared and tested in rabbits:

- Etonogestrel heptanoate
- Etonogestrel nonanoate
- Etonogestrel decanoate
- Etonogestrel undecanoate
- Etonogestrel dodecanoate
- Etonogestrel tridecanoate

Etonogestrel pentadecanoate was also prepared.

Figure 1 shows the chemical structure of these compounds.

As a reference, etonogestrel was also included.

Preparation of etonogestrel esters

General methodology for the preparation of esters from alcohols can be found in e.g. Greene, T.W. et al, "Protective groups in organic synthesis", John Wiley & Sons, NY, 1999 (third edition). Preparation of esters from tertiary alcohols (like etonogestrel) can be accomplished by several techniques, for instance: 1) tertiary alcohol, carboxylic acid, trifluoroacetic acid-anhydride, DE 1013284 (1956); 2) tertiary alcohol, acid chloride, pyridine, Watson, T.G. et al, Steroids 41, 255 (1983); 3) tertiary alcohol, acid chloride, TlOEt, Shafice, A. et al, Steroids 41, 349 (1983), 4) tertiary alcohol, carboxylic acid-anhydride, TsOH, benzene, Johnson, A.L., Steroids, 20, 263 (1972); and 5) tertiary alcohol, carboxylic acid-anhydride, DMAP, CH_2Cl_2, Shafiee, A. et al, Steroids 41, 349 (1983).

Preparation of (17α)-13-Ethyl-11-methylene-17-[[(1-oxononyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel nonanoate)

a) A solution of nonanoic acid (1.95 g) in dry toluene (8 ml) was cooled to 0 °C and treated with trifluoroacetic acid anhydride (2.6 g). After 30 min. stirring, (17α)-13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel, 2.0 g) in dry toluene (15 ml) was added and the reaction mixture was stirred for 17 h at room temperature. The reaction mixture was washed with water, a saturated aqueous solution of sodium hydrogen carbonate, water, and

brine. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography (toluene/ethyl acetate 95:5). The product (2.08 g) was dissolved in ethyl acetate (40 ml), cooled to 0 °C, and stirred with aqueous sodium hydroxide (1 M, 13 ml) for 2 h. The mixture was extracted with ethyl acetate; the combined organic phases were washed with ice-cold aqueous sodium hydroxide (1 M), water and brine, dried and concentrated under reduce pressure. Column chromatography afforded (17α)-13-ethyl-11-methylene-17-[[(1-oxononyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (1.25 g). ^{1}H-NMR ($CDCl_3$): δ 5.89 (m, 1H), 5.08 (bs, 1H), 4.85 (bs, 1H), 2.82 (ddd, 1H, J = 14.8, 9.5 and 6.3 Hz), 2.73 (d, 1H, J = 12.8 Hz), 2.69-2.19 (m), 2.63 (s, 1H), 2.11 (m, 1H), 1.90-1.21 (m), 1.15 (m, 1H), 1.05 (t, 3H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 465.3358. Calculated mass $[M+H]^+$ 465.3363.

In a manner analogous to the procedure described above, etonogestrel heptanoate, etonogestrel decanoate, etonogestrel undecanoate, etonogestrel dodecanoate, etonogestrel tridecanoate, and etonogestrel pentadecanoate were prepared:

b) (17α)-13-Ethyl-11-methylene-17-[[(1-oxoheptyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel heptanoate). ^{1}H-NMR ($CDCl_3$): δ 5.89 (m, 1H), 5.08 (bs, 1H), 4.85 (bs, 1H), 2.82 (ddd, 1H, J = 14.8, 9.5 and 6.3 Hz), 2.73 (d, 1H, J = 12.6 Hz), 2.68-2.19 (m), 2.63 (s, 1H), 2.11 (m, 1H), 1.90-1.24 (m), 1.15 (m, 1H), 1.05 (t, 3H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 437.3027. Calculated mass $[M+H]^+$ 437.3050.

c) (17α)-13-Ethyl-11-methylene-17-[[(1-oxodecyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel decanoate). ^{1}H-NMR ($CDCl_3$): δ 5.89 (bs, 1H), 5.08 (bs, 1H), 4.84 (bs, 1H), 2.82 (m, 1H), 2.73 (d, 1H, J = 12.6 Hz), 2.67-2.18 (m), 2.63 (s, 1H), 2.11 (m, 1H), 1.90-1.21 (m), 1.15 (m, 1H), 1.06 (t, 3H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 479.3508. Calculated mass $[M+H]^+$ 479.3519.

d) (17α)-13-Ethyl-11-methylene-17-[[(1-oxoundecyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel undecanoate). ^{1}H-NMR ($CDCl_3$): δ 5.89 (m, 1H), 5.08 (bs, 1H), 4.85 (bs, 1H), 2.82 (ddd, 1H, J = 14.8, 9.5 and 6.3 Hz), 2.73 (d, 1H, J =

12.6 Hz), 2.68-2.18 (m), 2.63 (s, 1H), 2.11 (m, 1H), 1.90-1.21 (m), 1.06 (t, 3H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 493.3664. Calculated mass $[M+H]^+$ 493.3676.

e) (17α)-13-Ethyl-11-methylene-17-[[(1-oxododecyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel dodecanoate). ^{1}H-NMR ($CDCl_3$): δ 5.89 (bs, 1H), 5.08 (bs, 1H), 4.85 (bs, 1H), 2.82 (m, 1H), 2.73 (d, 1H, J = 12.6 Hz), 2.65-2.18 (m), 2.64 (s, 1H), 2.11 (m, 1H), 1.90-1.20 (m), 1.15 (m, 1H), 1.06 (t, 3H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 507.3829. Calculated mass $[M+H]^+$ 507.3832.

f) (17α)-13-Ethyl-11-methylene-17-[[(1-oxotridecyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel tridecanoate). ^{1}H-NMR ($CDCl_3$): δ 5.89 (bs, 1H), 5.08 (bs, 1H), 4.85 (bs, 1H), 2.82 (m, 1H), 2.73 (d, 1H, J = 12.6 Hz), 2.65-2.18 (m), 2.64 (s, 1H), 2.11 (m, 1H), 1.90-1.20 (m), 1.15 (m, 1H), 1.06 (t, 3H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 521.4007. Calculated mass $[M+H]^+$ 521.3989.

g) (17α)-13-Ethyl-11-methylene-17-[[(1-oxopentadecyl)oxy]-18,19-dinorpregn-4-en-20-yn-3-one (etonogestrel pentadecanoate). ^{1}H-NMR ($CDCl_3$): δ 5.89 (bs, 1H), 5.08 (bs, 1H), 4.85 (bs, 1H), 2.82 (m, 1H), 2.73 (d, 1H, J = 12.6 Hz), 2.65-2.19 (m), 2.63 (s, 1H), 2.11 (m, 1H), 1.90-1.20 (m), 1.15 (m, 1H), 1.06 (t, 3H, J = 7.5 Hz), 0.89 (t, 3H, J = 7.1 Hz). Measured mass $[M+H]^+$ 549.4278. Calculated mass $[M+H]^+$ 549.4302.

Pharmacokinetics studies in the rabbit

For the determination of the pharmacokinetic profile of the different etonogestrel-esters after parenteral application, i.m. application in the castrated rabbit model was chosen instead of s.c. Briefly, rabbits were injected once (day 1) with indicated etonogestrel-esters at 20 mg/kg in arachis oil (with a concentration of 40 mg/ml). At day 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 21, 28, 35, 49, 63, 77, 92, 106, 120 and 133 blood was collected from the ear arteria, in EDTA-containing tubes. EDTA plasma was prepared (1500g, 15 min) and stored at -20°C. With LC-MSMS the amount of parent compound (etonogestrel) was determined in these samples. The lower limit of this new assay is 0.5 nmol/l, from 0-250 nmol/l a linear curve was obtained with a correlation coefficient of 0,9998.

As shown in Figure 2a, etonogestrel itself resulted in very high peak levels (200 nmol/l), which declined in 28 days to levels of etonogestrel below 1 nmol/l. Etonogestrel-heptanoate also gave rise to high initial peak levels of etonogestrel (120 nmol/l). Etonogestrel nonanoate gave lower peak levels and extended duration with serum levels of etonogestrel above 1 nmol/l. As compared to the other two esters in Figure 2a, etonogestrel undecanoate gave the most optimal balance between initial peak levels (maximum of 13 nmol/l after eight days) and duration of action (more than 92 days above 1 nmol/l).

As shown in Figure 2b, etonogestrel decanoate gave an initial peak level of 24 nmol/l after 5 days whereas etonogestrel dodecanoate gave an initial peak level of 9 nmol/l after 8 days. With etonogestrel tridecanoate, no initial levels of etonogestrel were observed.

From Figures 2a and 2b, it can be seen that preferred etonogestrel esters are etonogestrel decanoate, etonogestrel undecanoate, and etonogestrel dodecanoate.

CLAIMS

1. Etonogestrel undecanoate.

2. Etonogestrel decanoate.

3. A contraceptive and/or HRT kit comprising a contraceptively and/or therapeutically effective amount of etonogestrel undecanoate and/or etonogestrel decanoate and/or etonogestrel dodecanoate.

4. A kit according to claim 3 for male contraception and/or male HRT.

5. A kit according to claim 3 for female contraception and/or female HRT.

6. A use of a contraceptively and/or therapeutically effective amount of etonogestrel undecanoate and/or etonogestrel decanoate and/or etonogestrel dodecanoate for the preparation of a medicament for contraception and/or HRT.

7. A use according to claim 6 wherein the medicament is for male contraception and/or male HRT.

8. A use according to claim 6 wherein the medicament is for female contraception and/or female HRT.

9. A method of contraception and/or HRT comprising administering to a subject a contraceptively and/or therapeutically effective amount of etonogestrel undecanoate and/or etonogestrel decanoate and/or etonogestrel dodecanoate.

10. A method according to claim 9 wherein the subject is a male subject.

11. A method according to claim 9 wherein the subject is a female subject.

12. A use of a therapeutically effective amount of etonogestrel undecanoate and/or etonogestrel decanoate and/or etonogestrel dodecanoate for the preparation of a medicament for the treatment and/or prevention of a female gynaecological disorder.

13. A use according to claim 12 wherein the female gynaecological disorder is selected from the group consisting of endometriosis, menorrhagia, meno-metrorrhagia, pre-menstrual syndrome and dysmenorrhoea.

14. A method of treating and/or preventing a female gynaecological disorder comprising administering to a female subject a therapeutically effective amount of etonogestrel undecanoate and/or etonogestrel decanoate and/or etonogestrel dodecanoate effective to treat and/or prevent the disorder.

15. A method according to claim 14 wherein the female gynaecological disorder is selected from the group consisting of endometriosis, menorrhagia, meno-metrorrhagia, pre-menstrual syndrome and dysmenorrhoea.

16. Etonogestrel dodecanoate.

Figure 1

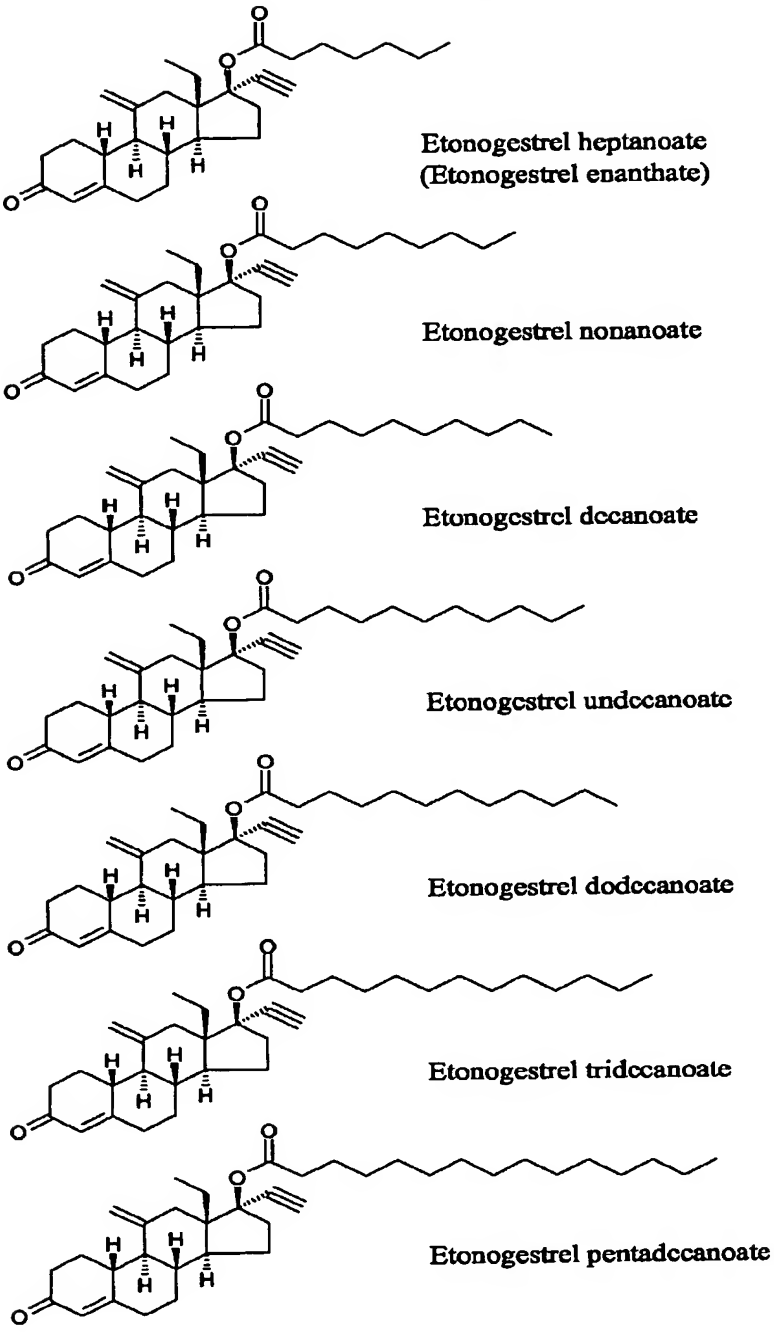
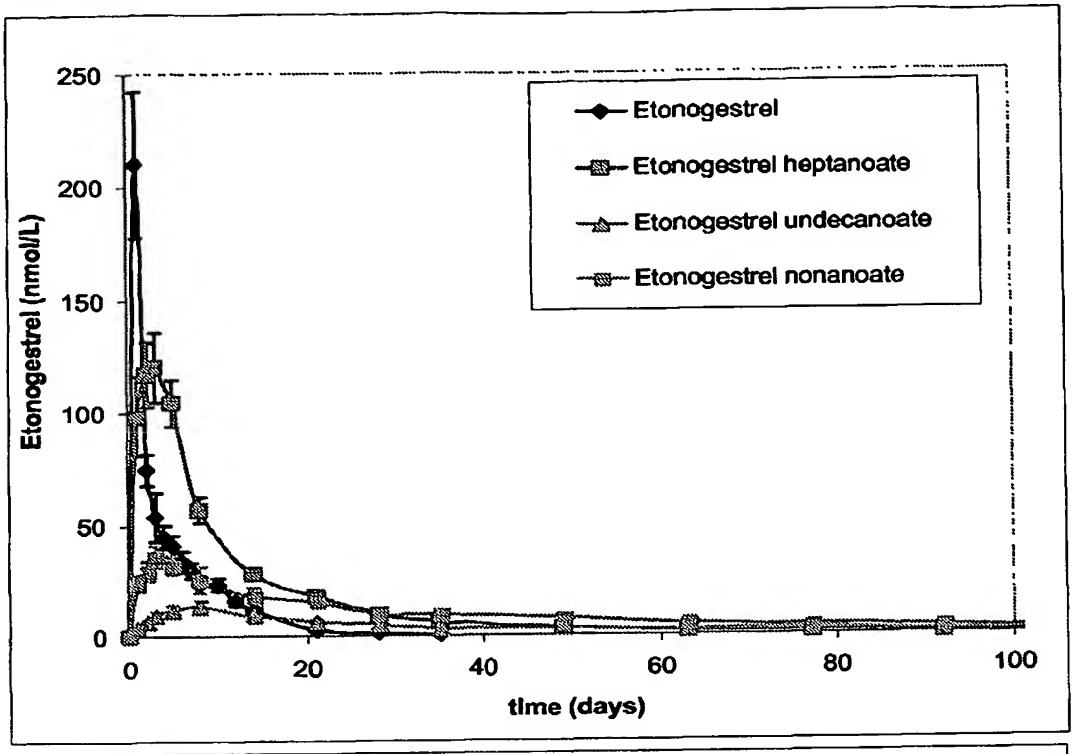
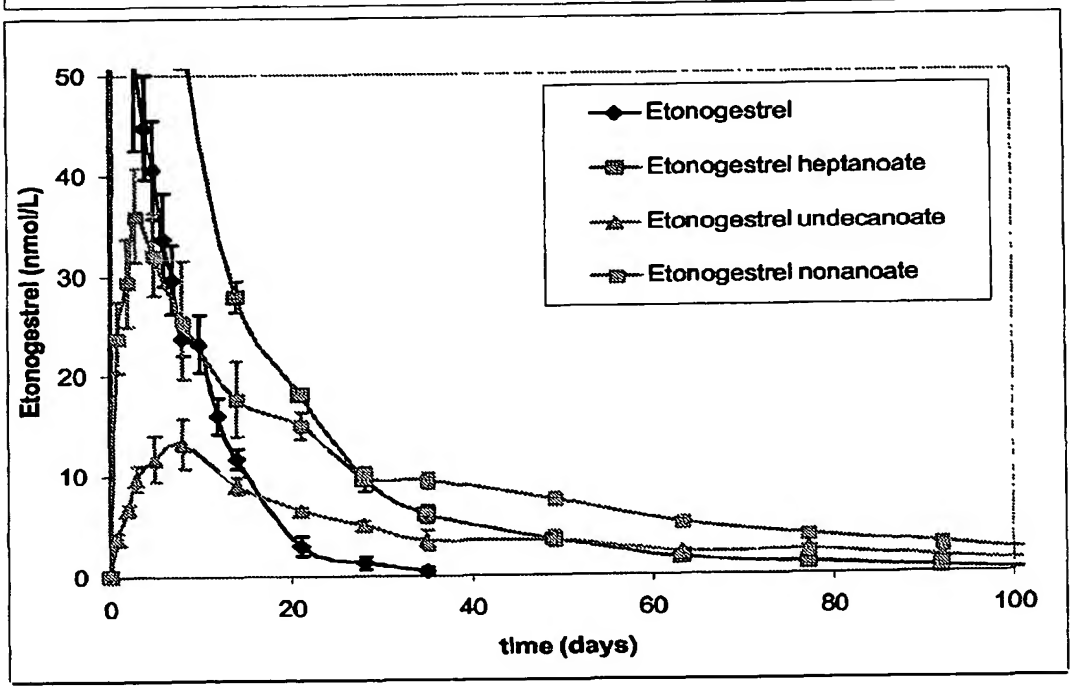

Etonogestrel heptanoate
(Etonogestrel enanthate)
Etonogestrel nonanoate
Etonogestrel decanoate
Etonogestrel undecanoate
Etonogestrel dodecanoate
Etonogestrel tridecanoate
Etonogestrel pentadecanoate

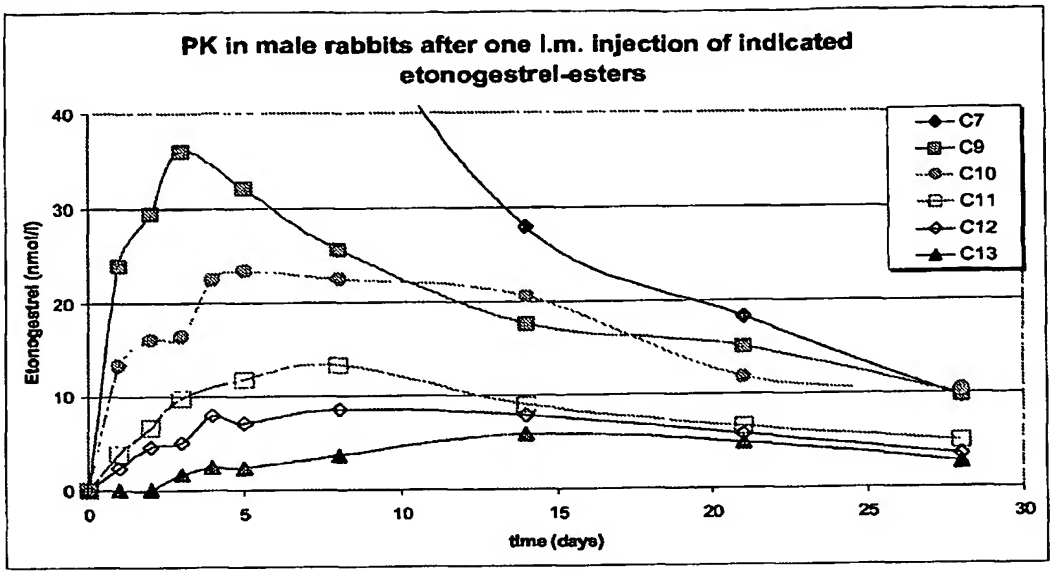
Figure 2a


Etonogestrel
Etonogestrel heptanoate
Etonogestrel undecanoate
Etonogestrel nonanoate
Etonogestrel (nmol/L)
time (days)
0
50
100
150
200
250
0
20
40
60
80
100


Etonogestrel
Etonogestrel heptanoate
Etonogestrel undecanoate
Etonogestrel nonanoate
Etonogestrel (nmol/L)
time (days)
0
10
20
30
40
50
0
20
40
60
80
100

5

Figure 2b



C7: Etonogestrel heptanoate

C9: Etonogestrel nonanoate

C10: Etonogestrel decanoate

C11: Etonogestrel undecanoate

C12: Etonogestrel dodecanoate

C13: Etonogestrel tridecanoate

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/50187

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J1/00 A61K31/565 A61P5/34 A61P15/16 A61P15/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 737 477 A (AKZO NOBEL NV) 16 October 1996 (1996-10-16) the whole document ---	1-10,16
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A	EP 0 129 947 A (WORLD HEALTH ORG) 2 January 1985 (1985-01-02) the whole document --- -/--	1,3

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2003	17/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	de Nooy, A

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International Application No
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